UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/518,931	03/03/00	GENTZ R	PF454P1

HM12/0227

JONATHAN L KLEIN
HUMAN GENOME SCIENCES INC
9410 KEY WEST AVENUE
ROCKVILLE MD 20850

EXAMINER	
O HARA, E	
ART UNIT	**PAPER NUMBER**
1646	14

DATE MAILED: 02/27/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/518,931	Gentz. et al.
Examiner	**Group Art Unit**
Eileen B. O'Hara	1646

☒ Responsive to communication(s) filed on *Dec 12, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *24-256* is/are pending in the applicat

Of the above, claim(s) *132-140 and 248-256* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *24-131 and 141-247* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *24-256* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5 and 11*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 24-256 are pending in the instant application.

Election/Restriction

2. Applicant's election with traverse of Group I, polypeptides, in Paper No. 13 is acknowledged. The traversal is on the ground(s) that restriction remains improper unless it can be shown that the search and examination of the groups together would entail a "serious burden", and Applicant asserts that no showing has been made and no arguments explaining why it would impose an undue burden to examine the polypeptide and antibody claims together, and the searches for polypeptides and antibodies against such polypeptides would clearly be overlapping. This is not found persuasive because consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search:. These criteria were met in the above restriction. A search for antibodies to a protein would constitute a different search than that of a search for the protein. It is old and well known in the art that antibodies have been generated without having purified protein, and antibodies to one protein may also cross-react with a related protein. As stated in the MPEP § 803, "a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP § 808.02.". Further, a search is directed not only to art which would be anticipatory, but also to art

that would render the invention obvious. Thus, the groups require divergent searches, and to search all inventions would be burdensome.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 132-140 and 248-256 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b).

Claims 24-131 and 141-247 will be examined on the merits.

Claim Objections

3.1 Claims 35, 76 and 102 are objected to because of the following informalities:

a) In claim 35, the word "is" is section (d) should be removed.

b) There is a semicolon instead of a period at the end of claim 76.

c) There is a period missing from the end of claim 102.

3.2 Claims 93-95, and 210-212 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4.1 Claims 46-75 and 141-192 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide comprising the amino acid of SEQ ID NO: 2, does not reasonably provide enablement for the polypeptide comprising the amino acid sequence of SEQ ID NO: 4, or for polypeptides that are 90 or 95% identical to the amino acid sequences SEQ ID NOS: 2 or 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification discloses two polypeptides which are splice variants, TNFR-6α, having the amino acid sequence shown in SEQ ID NO: 2, and TNFR-6β, having the amino acid sequence shown in SEQ ID NO: 4. TNFR-6α, which comprises 300 amino acid residues, and TNFR-6β, which comprises 170 amino acid residues, share the first 142 residues at the amino terminus. The specification further discloses that the TNFR-6α polypeptide binds two ligands in the TNF family of ligands, FasL and AIM-II, and can inhibit cell death induced by these ligands (pages 239-245), and can also inhibit apoptosis in livers of mice treated with Con A (pages 272-273). Therefore, the specification is enabled for the use of the full-length amino acid sequence of TNFR-6α, SEQ ID NO: 2. However, it is not predictable that the polypeptide comprising the

amino acid sequence of SEQ ID NO: 4, or that polypeptides that are 90% or 95% identical to the polypeptides of SEQ ID NOS: 2 and 4, would also have the same activities. The TNFR-6β polypeptide of SEQ ID NO: 4 shares 142 out of the 300 amino acids of SEQ ID NO: 2, and so has only 47% identity with that of TNFR-6α.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting

point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2). Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

4.2 Claims 35-45, 61-75, 89-101, 117-123, 152-162, 178-192, 206-218 and 233-239 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The enablement of claims 35-45, 61-75, 89-101, 117-123, 152-162, 178-192, 206-218 and 133-139 requires availability of the specific plasmids claimed therein. This determination

has been made because said plasmids are not fully disclosed nor have they been shown to be publicly known and freely available. Accordingly, it is deemed that deposits containing these plasmids should have been made in accordance with MPEP Chapter 2400 and 37 C.F.R. §§ 1.801-1.809. The Examiner acknowledges the deposit of plasmids HPHAE52 and HTPCH84 accorded under ATCC No.978210 and 978209, respectively (see page 13 of the specification). An affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 219-232 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 219-232 are indefinite because claim 219 has sections, a, b, i, j, k, l and m, are missing sections c-g, which are referred to in the dependent claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 24-29, 31, 33, 35-40, 42, 44, 46-55, 57, 59, 61-70, 72, 74, 76-83, 85, 87, 89-96, 98, 100, 102-111, 113, 115, 117, 118, 120, 122, 124, 125, 126, 128, 130, 206, 208, 209, 211-213, 215, 217, 219-224, 226, 227, 229, 231, 233, 234, 236, 238, 240-242, 244 and 246 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Emery et al., PN 5,885,800, March 23, 1999 (cited by Applicant).

These claims encompass an isolated polypeptide comprising an amino acid sequence of SEQ ID NO: 2 or 4, comprising a heterologous polypeptide, wherein the polypeptide is glycosylated, a composition comprising the polypeptide, amino and carboxy terminal truncations of the polypeptide and polypeptides comprising 30 and 50 contiguous amino acids and epitope-bearing fragments of SEQ ID NOS: 2 and 4.

Emery et al. disclose a polypeptide having the amino acid sequence shown in SEQ ID NO: 2, which is 100% identical to SEQ ID NO:2 of the instant application, and 100% identical to amino acids 1-142 of SEQ ID NO:4 of the instant application. Emery et al. teach that the polypeptide and fragments thereof can be modified by glycoslyation (column 4, line 22), may be

in the form of fusion proteins (column 5, lines 37-44), can be truncated from the amino or carboxy terminal ends (column 5, lines 59-65), are present in formulations (column 14, lines 30-48), and antigenic or immunogenic fragments (column 6, lines 6-11). Therefore, Emery et al. anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7.1 Claims 32, 43, 58, 73, 86, 99, 114, 121, 129, 216, 230, 237 and 245 are rejected under 35 U.S.C. 103(a) as being unpatentable over Emery et al., PN 5,885,800, March 23, 1999, as applied to claims 24-29, 31, 33, 35-40, 42, 44, 46-55, 57, 59, 61-70, 72, 74, 76-83, 85, 87, 89-96, 98, 100, 102-111, 113, 115, 117, 118, 120, 122, 124, 125, 126, 128, 130, 206, 208, 209, 211-213, 215, 217, 219-224, 226, 227, 229, 231, 233, 234, 236, 238, 240-242, 244 and 246 above, and further in view of Shadle et al., PN 4,847,325, July 11, 1989.

Claims 32, 43, 58, 73, 86, 99, 114, 121, 129, 216, 230, 237 and 245 encompass polypeptides of SEQ ID NOS: 2 and 4 which are pegylated. The teachings of Emery et al. are summarized as above. Emery et al. does not disclose that said polypeptide may be pegylated.

Shadle et al., teach that the half-lives of polypeptides in blood of animals can be increased by chemical modification by conjugation to a polymer such as polyethylene glycol (PEG), and that conjugation to PEG can also reduce the immunogenicity of the protein (column 2, line 27 to column 3, line 38, and column 4, line 26- column 5, line 9). Therefore, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use Emery's protein and to conjugate it to PEG, as taught by Shadle et al., in view of Shadle et al.'s suggestion that it would be desirable to do so, as cited above. One of skill would be motivated to do so in order to increase the half-life of the protein and to reduce immunogenicity, and would have a reasonable expectation of success since this was a common method at the time the invention.

7.2 Claims 30, 34, 41, 45, 56, 60, 71, 75, 84, 88, 97, 101, 112, 116, 119, 121, 123, 127, 131, 214, 218, 228, 232, 235, 239, 243 and 247 are rejected under 35 U.S.C. 103(a) as being unpatentable over Emery et al., PN 5,885,800, March 23, 1999, as applied to claims 24-29, 31, 33, 35-40, 42, 44, 46-55, 57, 59, 61-70, 72, 74, 76-83, 85, 87, 89-96, 98, 100, 102-111, 113, 115, 117, 118, 120, 122, 124, 125, 126, 128, 130, 206, 208, 209, 211-213, 215, 217, 219-224, 226, 227, 229, 231, 233, 234, 236, 238, 240-242, 244 and 246 above, and further in view of Rosen et al., PN 5,985,614, Nov, 16, 1999.

Claims 30, 34, 41, 45, 56, 60, 71, 75, 84, 88, 97, 101, 112, 116, 119, 123, 127, 131, 214, 218, 228, 232, 235, 239, 243 and 247 encompass polypeptides of SEQ ID NOS: 2 and 4 which

comprise a heterologous polypeptide which is an Fc domain of immunoglobulin or which are part of a composition comprising a liposome. The teachings of Emery et al. are summarized as above. Emery et al. does not disclose that said polypeptides comprising a heterologous polypeptide which is an Fc domain of immunoglobulin or which are part of a composition comprising a liposome.

Rosen et al., teach that polypeptides may be expressed in a modified form such as a fusion protein which may contain the Fc domain of Immunoglobulin (column 14, lines 1-35), and that the polypeptides have be administered in the form of liposomes (column 23, lines 14-28). Therefore, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use Emery's protein and to make a fusion protein with the Fc domain, or to make a composition of the polypeptide in a liposome, as taught by Rosen et al. One of skill in the art would be motivated to do so in view of Rosen et al.'s suggestions that it would be desirable to make an Fc fusion in order to facilitate purification of the protein, or to solubilize protein, or to improve pharmacokinetic properties, and to make liposome compositions to facilitate therapeutic administration. One of skill would have a reasonable expectation of success since these were common and successful methods of modifying proteins at the time the invention.

Conclusion

8.1 No claims are allowed.

8.2 The full length polypeptide of SEQ ID NO: 4 is free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D

Patent Examiner

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER